Long-term follow-up of lung transplant recipients supports non-operative treatment of uncomplicated diverticulitis

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Abstract: BACKGROUND: We aim to assess the incidence, current treatment, and outcome of diverticulitis in highly immunosuppressed lung transplant recipients. METHODS: Retrospective analysis of a prospective database of 403 lung transplant recipients transplanted between 1992 and 2013 with a mean follow-up of 100 months (SD 58.0). RESULTS: 4.46% of lung transplant recipients (n=18) developed diverticulitis. Eight lung transplant recipients developed uncomplicated diverticulitis, which were all treated successfully with antibiotics. Three patients (37.5%) underwent elective sigmoid resection with severe Grade 3b complications after two of five (40%) surgical procedures. Diverticulitis recurrence occurred in five patients (60%). In total, 10 lung transplant recipients presented with 11 episodes of perforated diverticulitis with a 30-day mortality rate of 9.1%. Hartmann procedure was performed in eight lung transplant recipients. Sigmoid resection with primary anastomosis and protective ileostomy was performed in three patients with Hinchey I. Two of these patients developed anastomotic leakage with a secondary Hartmann procedure. CONCLUSION: Due to high leakage rate after resection with primary anastomosis and protective ileostomy in our cohort of lung transplant recipients with perforated diverticulitis, the Hartmann procedure seems to be the safer option. In contrast, in uncomplicated diverticulitis, non-operative treatment can be considered as a safe and highly successful treatment option, even for recurrences.

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Long-Term Follow-Up of Lung Transplant Recipients Supports Non-Operative Treatment of Uncomplicated Diverticulitis

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Diverticulitis in lung transplant recipients

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List of Abbreviations:

LTRs - lung transplant recipients

HP- Hartmann’s procedure

Title

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Abstract

Background: We aim to assess the incidence, current treatment and outcome of diverticulitis in highly immunosuppressed lung transplant recipients. **Methods**: Retrospective analysis of a prospective database of 403 lung transplant recipients transplanted between 1992 and 2013 with a mean follow-up of 99 months (SD 58.0). **Results:** 4.46% of lung transplant recipients (n=18) developed diverticulitis. Eight lung transplant recipients developed uncomplicated diverticulitis, which were all treated successfully with antibiotics. Three patients (37.5%) underwent elective sigmoid resection with severe Grade 3b complications after two of five (40%) surgical procedures. Diverticulitis recurrence occurred in five patients (60%). In total 10 lung transplant recipients presented with 11 episodes of perforated diverticulitis with a 30-day mortality rate of 9.1%. Hartmann procedure was performed in 8 lung transplant recipients. Sigmoid resection with primary anastomosis and protective ileostomy was performed in 3 patients with Hinchey I. Two of these patients developed anastomotic leakage with a

secondary Hartmann procedure. **Conclusion:** Due to high leakage rate after resection with primary anastomosis and protective ileostomy in our cohort of lung transplant recipients with perforated diverticulitis, the Hartmann procedure seems to be the safer option. In contrast, in uncomplicated diverticulitis non-operative treatment can be considered as a safe and highly successful treatment option, even for recurrences.

Keywords

lung transplantation, colon perforation, diverticulitis, immunosuppression, Hartmann procedure

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Introduction

Diverticular disease is a very common condition in Western societies with increasing prevalence. Complications of diverticular disease are acute uncomplicated diverticulitis and complicated diverticulitis including perforation as well as diverticular bleeding (1). To date, limited data is available on the natural history of diverticulitis in immunosuppressed patients. The incidence of acute diverticulitis appears higher in immunosuppressed patients and development of complicated disease seems more likely (2, 3).

It remains unclear, whether the recurrence rate after an uncomplicated episode is also higher in this population. A recent study found no difference in recurrence rate and the authors did not detect a significant difference in emergency surgery for recurrent disease in immunosuppressed vs. non-immunosuppressed patients(4). However, current guidelines recommend a low threshold for early elective surgery in immunosuppressed patients(5). Mortality and morbidity in emergency surgery have been shown to be significantly higher in immunosuppressed organ transplant recipients compared to their matched controls (3). These differences in mortality or morbidity were not observed following elective surgery in immunosuppressed patients with diverticulitis (3). This was supported by data from a large nationwide retrospective review of colorectal surgeries in kidney transplant recipients, showing a low mortality and morbidity in kidney transplant patients undergoing colorectal surgery (6). This might be due to a better preoperative health compared to other solid organ recipients as well as the need for intensified immunosuppression after heart or lung transplantation compared to kidney transplantation (3).

Receiving intensified (triple-) immunosuppression and given their close follow-up and the availability of data, we aimed to study the natural history of diverticulitis in lung transplant recipients. Specifically we aimed to critically analyze the paradigm to keep a low threshold for elective surgery in uncomplicated diverticulitis in immunosuppressed patients.

Materials and Methods

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Data

We retrospectively analyzed the prospective database of 403 lung transplant recipients at our institution between January 1992 and December 2013 and assessed patients with perforated and uncomplicated diverticulitis. We analyzed age, gender, symptoms at time of diagnosis, time from lung transplant to colonic complication, time from onset of symptoms to treatment, laboratory values, radiologic findings, degree of colon complication, treatment of colonic complication, immunosuppression at presentation, change of immunosuppressive treatment, antibiotic treatment pre- and post- diagnosis, non-operative or surgical treatment strategy, morbidity, hospital stay, length of follow up and 30-day mortality. We also evaluated whether colonoscopies were performed prior to transplantation to assess preexisting diverticular disease.

Definitions

All lung transplant recipients with spontaneous lower abdominal pain and/ or tender abdomen upon palpation received either a CT scan or an MRI

for further workup. The diagnosis was made when inflamed diverticula with inflamed surrounding fatty tissue were detected on a CT-scan or MRI(7). In one patient diagnosis of a recurrent episode of non-perforated diverticulitis was based on clinical presentation, x-ray and sonography. We considered diverticulitis with any extraluminal air in the imaging as perforated diverticulitis. In contrast we defined diverticulitis without signs of perforation as uncomplicated diverticulitis episodes.

Statistical analysis

All mean values and standard deviations (8) as well as median values and range measurements were calculated by Microsoft excel for Mac 2011, Version 14.3.9. Data are expressed as mean with SD or median with range. Mann-Whitney-U tests were performed to compare the experimental groups. Differences were considered statistically significant if $p<0.05$. Analyses were conducted using Graph Pad prism Version 4.0b.

Results

Patient demographics and incidence of diverticulitis

Between November 1992 and December 2013 a total of 18 of 403 lung transplant recipients (4.47%) developed diverticulitis during a mean follow up (FU) after transplantation of 99.8 months (SD 58.0) (median 110 months; range 9-208), as diagnosed by CT scan or MRI (Suppl Table 1A,1B). Our local transplant unit requires colonoscopy as part of pretransplant workup only in patients 50 years and older or in individuals with gastrointestinal complaints or positive family history for intestinal disease. Thus only 5/18 patients underwent a colonoscopy before transplantation, which documented a diverticulosis in all five cases. However, none of the 18 patients had experienced an episode of diverticulitis before transplantation. Ten of 18 lung transplant recipients with diverticulitis had 11 episodes of perforated diverticulitis at a mean time of 60.6 months (SD 66.3) after lung transplantation (Table 3). Perforations occurred within 1 year of transplantation in 36.4% (4/11) of cases. The mean age at the time of diverticular perforation was 59.4 years (SD 7.0) (Table 3). Mean FU after colonic perforation was 27.9 months (SD 42.2) (Table 3). At presentation one of these patients was hypotensive and required catecholamines. The remaining cases were normotensive. Two of eleven patients were tachycardic and two patients had fever (>38.5°C). Time from symptoms to treatment varied between 0.5 days and 3 days (mean 1.65 days, SD 1.0). The reason for transplantation were Langerhans-Histocytosis (n=1), pulmonary

emphysema due to AT1-deficiency (n=6), endstage COPD (n=1), severe pulmonary hypertension (n=1) and cystic fibrosis (n=1).

In addition, eight lung transplant recipients had 12 episodes of uncomplicated diverticulitis at a mean FU of 122.8 months (SD 30.0) post transplant. The average age of these patients at time of the diverticular episode was 63 years (Table 3). Mean FU after uncomplicated diverticulitis episode was 61.7 months (SD 23.9) (Table 3). Patients with uncomplicated diverticulitis were normotensive (n=5) or hypertensive (n=7). Two patients with uncomplicated disease presented with fever. Time between symptoms and treatment varied between 0.5 and 6 days (mean 2.31 days, SD 1.95).

The underlying diagnoses leading to lung transplantation in patients with uncomplicated diverticulitis were chronic obstructive lung disease (n=4), alpha-1-AT-deficiency with lung emphysema (n=2), idiopathic lung fibrosis (n=1), and Kartagener-Syndrome (n=1).

With exception of one patient who received tacrolimus instead of cyclosporine due to insufficiently controllable drug levels within the first month after transplantation, all patients received cyclosporine, mycophenolate and prednisone (Table 4). The immunosuppression regime did not change over time. Immunosuppression was not routinely changed upon the diagnosis of diverticulitis. However, in case of expected surgical intervention we routinely reduced mycophenolate by 1/3 to 1/2 of the dose. If differential blood count showed a trend towards cytopenia we further reduced the mycophenolate dose to avoid neutropenia (9).

Treatment and Outcome of Complicated Diverticulitis

Of the 10 patients presenting with 11 episodes of perforated diverticulitis all were treated surgically. HP was performed in 8 patients with Hinchey I(n=1), II(n=1), III(n=3) and IV(n=3). The remaining 3 cases all with Hinchey I(n=3) had a colonic resection with anastomosis and protective ileostomy in 2/3 cases. Two of these three cases occurred in the same patient with 32 months between both resections. Due to the short interval between the two episodes, the reason for recurrence is most likely an incomplete resection of the high-pressure zone. While the primary anastomosis healed in the first episode, a leakage of the descendorectostomy occurred six days after the second surgery, necessitating an end colostomy. The third patient was primarily treated with a diagnostic laparoscopy, lavage and drainage followed by resection with primary anastomosis six days later. This patient developed an anastomotic leakage four days later, which required a resection with end-colostomy. Although the three cases treated with primary anastomosis only had a Hinchey stage I diverticulitis, two required a secondary HP due to anastomotic leakage (Table 1). Taken together, 91% (10/11) of the cases with a perforated diverticulitis received a HP and two out of three (66.7%) patients with a primary anastomosis developed a major grade 3b complication according to the Clavien-Dindo Classification(10) after resection and anastomosis. No organ failure or death occurred, however. Of the 8 patients primarily treated with HP five (63%) developed a severe (≥grade 3b) complication. Single or multiorgan failure occurred in three patients (grade 4a,b) and one patient died (grade 5) within 30 days resulting in a 30-day mortality of 9.1% after perforated sigmoid diverticulitis. Another two patients died within 2 and 4.5 months after surgery (Table 1).

Overall median hospital stay amounted to 24.5 days (range 14-133), with a median length of stay of 41 days (range 14-133) in patients with HP versus 24 days (range 23-27) in the patients primarily treated with anastomosis.

Thus in our experience of 3 cases, performing a primary anastomosis in highly immunosuppressed patients with a perforated sigmoid diverticulitis, even in Hinchey I situations, the risk for anastomotic leakage is extremely high.

Colostomy reversal

Only 20% (2/10) of patients with colostomy have had a reversal of the colostomy at 16 and 7 months after the primary surgery within a mean FU of 21.9 months (SD 40.5) after primary or secondary HP. Of the two colostomy reversals one had postoperative self-limiting anal bleeding without endoscopic signs of leakage (grade 1 complication). In the second patient with colostomy reversal and in one patient with ileostomy reversal no complications occurred. None of these patients died upon reversal. Of the remaining 8 patients 3 died and 5 still had a colostomy at the end of our observation period, which was at a mean of 8.3 months (SD 5.8) after the HP. Thus, only a minority of patients have a colostomy reversal with a reasonable postoperative morbidity.

Treatment and Outcome of Uncomplicated Diverticulitis

Of the 8 LTRs with uncomplicated diverticulitis all were treated successfully with broad spectrum i.v. antibiotics and oral food intake restriction. Three of these patients received elective resection at a mean of

2.25 months after the diverticulitis episode. Of the remaining 5 patients, 3 (60%) developed an uncomplicated recurrence within 1 (n=2) and 8.5 months (n=1). One patient developed another uncomplicated re-recurrence 27 months later. All recurrences were again successfully treated with antibiotics (Figure 1). There were no complications during the hospitalization with a mean hospitalization time of 10.7 days (SD 4.3).

Thus, we found a high recurrence rate of uncomplicated diverticulitis in lung transplant recipients, all of which were treated successfully with i.v. antibiotics.

Two of three patients with an elective resection underwent a laparoscopic resection with primary anastomosis and protective ileostomy and one patient had an open resection with primary anastomosis. Both ileostomies were reversed at 2.5 and 5.5 months after placement. One stoma prolapse and one anastomotic insufficiency upon ileostomy reversal occurred, both requiring surgery.

Thus, after three elective sigmoid resections and two subsequent elective ileostomy-reversals, two (40%) 3b complications occurred (Figure 2). The involved surgeons were all board certified according to the federation of swiss surgeons (FMH) and had been consultants at the abdominal surgery department of the University Hospital of Zurich for at least 4 years at the time of surgery.

The mean total hospitalization duration of these patients with elective surgical treatment was 39.3 days (SD 34). This was not significantly different from the mean hospitalization time of 26 days (SD 17.4) in the patients with

uncomplicated diverticulitis without elective resection, when recurrence and bleeding episodes were included (p=0.39) (Table 2).

Of note, one patient with elective laparoscopic resection, protective ileostomy and ileostomy reversal with an entirely uneventful course presented with a rectum perforation most probably due to a perforated diverticulum 6 years after sigmoid resection.

Discussion

In this monocentric study we analyze the incidence and outcome of sigmoid diverticulitis in a large number of lung transplant recipients with a long follow-up and no loss to follow-up. Our study includes complicated- and uncomplicated diverticulitis and thus surgical- and non-surgical treatment, giving an idea of the natural history of the disease in immunosuppressed patients. During a mean follow-up of 8.3 years, 4.5% of our lung transplant recipients developed diverticulitis. This corresponds to an extrapolated incidence of 550 per 100,000 lung transplant recipients, which is about 15 times higher than in the non-immunosuppressed population, where diverticulitis is responsible for approximately 25 to 50 hospital admissions per 100,000 people per year(11),(12). The diverticulitis rate is identical to a recently published paper on diverticulitis in lung transplant recipients with a short follow-up of 442 days (4.5%)(13) and higher than in pooled data from other transplanted organs, where it was 1.7%(14). This may be due to the lower level of immunosuppression compared to other types of organ transplantation. Furthermore, consistent with previous data in immunosuppressed patients(2),(15) the majority (55.6%) of our lung transplant recipients presented with perforated sigmoid diverticulitis at their first episode as opposed to the non-immunosuppressed population where only 37.7%(16) of patients have been shown to present with perforation at their initial episode. Time from symptoms to treatment was not longer in the complicated- versus the uncomplicated diverticulitis group and the majority of patients even with complicated diverticulitis were normotensive, afebrile and cardiopulmonary stable. Thus, we exclude deterioration of an initially

uncomplicated diverticulitis as cause for this relatively high prevalence of complicated disease. This is in line with the theory, that complicated- and uncomplicated diverticulitis are etiologically two different diseases (17, 18).

All patients with perforated sigmoid diverticulitis were treated surgically. Interestingly, despite a positive selection of patients with Hinchey I diverticulitis receiving a primary anastomosis, primary anastomosis failed in two of three cases, ultimately leading to a HP rate of 90.9%. This suggests that immunosuppressed patients with perforated diverticulitis irrespective of their Hinchey stage may benefit from a discontinuity resection.

In the non-immunosuppressed population, selection criteria of patients for elective sigmoid resection after an uncomplicated episode of diverticulitis remain unclear. Recent studies have shown that patients with more than two episodes are not at an increased risk for complications as compared to patients with fewer episodes(19). In contrast, in transplant patients non-operative treatment - including antibiotics and short term food restriction - is thought to have a high failure rate, leading to a high mortality(2). In our population 37.5% (3/8) of lung transplant recipients received an elective sigmoid resection after the first episode of uncomplicated diverticulitis, as compared to around 7%(20) of non-immunosuppressed patients. Our policy to have a low threshold for elective surgery following the first episode of uncomplicated diverticulitis in immunosuppressed patients is in line with the current recommendation of the ASCRS(5). However, the analysis of our lung transplant recipient cohort does not seem to support this practice for the following reasons: Firstly, although the recurrence rate after the first

uncomplicated diverticulitis in lung transplant recipients was higher than in the non-immunosuppressed population (60% vs. 13%- 20%) (20), all recurrences were successfully treated with i.v. antibiotics, with no additional morbidity other than re-recurrence and diverticular bleeding in two patients. In particular none of the patients presented with perforation at a further episode of diverticulitis. Secondly, lung transplant recipients with elective resection required up to two elective surgical procedures (e.g resection and stoma reversal). Importantly, additional emergency surgery was required in two of five elective procedures due to grade 3b complications. Furthermore, surgical treatment did not reduce total hospitalization time and lastly, as mentioned above resection could not fully prevent a second episode with perforation.

The observation, that elective procedures in immunosuppressed patients with organ transplantation have a high morbidity in the elective setting is not in line with previous studies that found no difference in morbidity or mortality after elective colorectal surgeries in organ recipients as compared to matched controls (3). Further, none of our patients with uncomplicated diverticulitis presented with a perforated diverticulitis to a later timepoint. Although in other studies the percentage was low, it was not zero (3).

In conclusion, the results of our study have to be interpreted with caution given the small number of patients. However, in line with the current literature and recommendations, our data confirms the higher incidence of diverticulitis-, as well as the higher rate of perforated diverticulitis in lung transplant recipients. Due to high leakage rate after resection with primary anastomosis and protective ileostomy in our cohort of lung transplant recipients with perforated diverticulitis the Hartmann procedure may be the safer option. In

contrast to previous findings we observed that uncomplicated diverticulitis in lung transplant recipients can be successfully treated using a non-operative approach even in recurrences thus avoiding morbidity of elective surgery. Ultimately, these findings might change recommendations towards a higher threshold for elective surgery in immunosuppressed patients. Bigger studies evaluating the risk of perforation at recurrence against the morbidity of elective surgery, as well as more data on the role of primary anastomosis in lung transplant recipients with perforated diverticulitis are needed to ultimately answer these questions.

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Authors' Contributions

- **Diana Vetter:** acquisition of data, analysis of data and writing of the manuscript
- **Macé M Schuurmans:** access to data of lung transplant recipients, help in conception and design of the manuscript, as well as revising of manuscript.
- **Christian Benden:** access to data of lung transplant recipients, as well as editing of the manuscript.
- **Pierre-Alain Clavien:** important input on study focus and editing of the manuscript
- **Antonio Nocito:** idea of the study, interpretation of data, drafting the article and critical revision of the manuscript

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